REMARKS

Reconsideration of the present Application in view of the Amendments and Request for Continued Examination enclosed herewith and the following remarks is respectfully requested. Applicants have amended claim 19 to particularly point out and distinctly claim certain embodiments of Applicants' invention. Applicants hereby cancel claims 3, 4, 6, 9-17, and 20. For additional clarity, so that dependent claims follow independent claim 19 in numerical order, claims 3, 4, 6, and 9-17 have been cancelled and new claims 24-35 have been added that recite the subject matter previously recited in the cancelled claims. The above Amendments are submitted without acquiescence to any rejection and without prejudice to prosecuting any cancelled or removed subject matter in a related divisional, continuation, or continuation-in-part application. No new subject matter has been added to the application. Support for amended claim 19 may be found throughout the application, for example, at page 21, lines 4-17. Accordingly, upon entry of this amendment, claims 19 and 21-35 are pending.

Rejections Under 35 U.S.C. § 103

Part I. In the Office Action dated May 10, 2006, the Examiner rejected claims 3, 4, 6, 10, 11, 16, 17, 19, and 21-23 under 35 U.S.C. § 103(a) for allegedly being obvious over U.S. Patent No. 5,726,292 ('292) or Lowell (*Science* 240:800-802 (1988)) (referred to herein as the Lowell article) in view of VanCott (VanCott et al., *J. Immunol. Meth.* 183:103-117 (1995)) and further in view of International Patent Application Publication No. WO 95/11700.

Part II. The Examiner rejected claim 9 under 35 U.S.C. § 103(a) for allegedly being obvious over '292 or the Lowell article in view of WO 95/11700, and further in view of VanCott and Desai (Desai et al., *Proc. Natl. Acad. Sci. USA* 83:8380-8384 (1986)).

Applicants respectfully traverse this rejection and submit that the present claims meet the requirements for nonobviousness under 35 U.S.C. § 103. Each of the cited documents alone or in any combination fails to teach or suggest an immunogenic composition that comprises (1) an antigen comprising a truncated gp160 protein that (a) is truncated at the C-terminal end such that the truncated gp160 protein has a molecular mass of about 140 kDa, and

(b) comprises the endogenous hydrophobic amino acid sequence set forth at positions 523-551 of SEQ ID NO:1; (2) proteosomes that are complexed or coupled with the antigen; and (3) bioadhesive nanoemulsions, wherein the composition elicits neutralizing antibodies to HIV in a subject that are present in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces.

The exemplary truncated gp160 polypeptide described in the present application lacks approximately 50% of the gp41 moiety of gp160. By contrast, none of the cited documents alone or in any combination teaches or suggests an immunogenic composition that comprises a truncated gp160 protein having a molecular mass of about 140 kDa that is truncated at the carboxy terminal end. Each cited document fails to teach or suggest that portions of the gp160 may be removed and that the remaining portion would be useful as an immunogenic composition when combined with proteosomes. Instead, each of the cited documents describes use of full-length gp160 as an immunogen or describes use of an unrelated antigen as an immunogen. Moreover, none of the cited documents alone or in any combination provides any motivation, teaching, or suggestion to alter the gp160 polypeptide to achieve the claimed immunogenic composition.

Applicants respectfully disagree with the Examiner's assertion that the present composition is obvious further in view of VanCott and that VanCott inherently teaches the use of the truncated gp160 antigen. VanCott and Kalyanaraman et al. (*AIDS Res. Hum. Retroviruses* 4(5):319-329 (1988)), to which the Examiner refers, *explicitly* teach that the gp160 described therein is a full-length gp160 (*see, e.g.,* Kalyanaraman et al. at page 322-324; *see also* specification at page 21, lines 18-23). Accordingly, a person having ordinary skill in the art could have no reasonable expectation of successfully obtaining the claimed compositions on the basis of the teachings in VanCott in combination with any of the cited documents.

Even assuming, *arguendo*, that a person having ordinary skill in the art were able to intuit from VanCott that an immunogenic composition may comprise a truncated gp160 protein as recited, a person having ordinary skill in the art would have no reasonable expectation that a truncated gp160 antigen could be combined with proteosomes and bioadhesive

nanoemulsions to form an immunogenic composition useful for eliciting neutralizing anti-HIV antibodies that are present in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces. Furthermore, '292 points out that gp160 is a transmembrane polypeptide and further describes that the presence of a hydrophobic moiety, such as the transmembrane region of gp160, may be sufficient such that gp160 would form a complex with proteosomes (*see, e.g.,* column 13, lines 43-48; column 18, line 21; column 20, lines 12-16). Because the carboxy terminal truncation of gp160 in the transmembrane gp41 portion would remove one or more hydrophobic portions of transmembrane gp41, a person having ordinary skill in the art would reasonably expect that to complex the truncated gp160 polypeptide with proteosomes would require that an exogenous hydrophobic moiety be added to the truncated gp160 to anchor the polypeptide to the proteosomes.

As described in the present application, however, the truncated gp160 polypeptide without an exogenous hydrophobic portion and in combination with proteosomes was an immunostimulating composition (*see, e.g.,* pages 50-51). The '292 patent does not teach or suggest an antigen comprising a C-terminal truncated gp160 protein that has a molecular mass of about 140 kDa and that comprises the endogenous hydrophobic amino acid sequence set forth at positions 523-551 of SEQ ID NO:1, which lacks the transmembrane region of the gp41 portion. The '292 patent also fails to teach or suggest that the HIV antigen described therein when complexed with proteosomes and administered to a subject will elicit neutralizing antibodies that are detected in at least one of vaginal secretions, intestinal secretions, lung secretions, and feces. Lowell instead teaches that intramuscular injection of full-length gp160 in combination with proteosomes induces production of serum IgG antibodies that bind to gp160 and to gp41. The Lowell article teaches an immunogenic composition that comprises proteosomes and antigens unrelated to gp160 or any HIV antigen, specifically, malarial peptide antigens.

The published application, WO 95/11700, also fails to teach or suggest a truncated gp160 antigen complexed with proteosomes and combined with bioadhesive nanoemulsions that elicits neutralizing antibodies detected in at least one of vaginal secretions, intestinal secretions, lung secretions, and feces. WO 95/11700 instead teaches that parenteral

administration of full-length gp160 in combination with submicron emulsions with and without proteosomes increases the titer in sera to gp120 and gp41 epitopes.

In the HIV art, the antigenicity of the *env* gene products, the precursor gp160 and the mature gp120 and gp41 polypeptides, has been long recognized, and so has the difficulty in identifying one or more epitopes of these envelope proteins that would be useful for immunizing humans against multiple subtypes of HIV (*see, e.g.,* VanCott, Introduction and references cited therein). Moreover, in the absence of the present application describing an immunogenic composition comprising the truncated gp160 polypeptide, as recited, for inducing a neutralizing antibody response against HIV in a subject, a person having ordinary skill in the art would not reasonably expect to obtain Applicants' claimed invention. The nonobviousness of the presently claimed process is evidenced by VanCott et al. (*J. Immunol.* 160:2000-2012 (1998), submitted herewith), who demonstrated that the combination of proteosomes with truncated gp160 was a significantly improved immunogenic composition compared with full-length gp160 complexed with proteosomes (*see* VanCott et al., page 2008, first column; page 2009, Table IV). In mice, full-length gp160 elicited neutralizing IgG and IgA that were detected in sera; however, only mice immunized with truncated gp160 (therein referred to as gp451) elicited neutralizing antibodies in mucosal secretions. VanCott et al. concluded that their findings demonstrated "the importance of both adjuvant and protein structure in eliciting mucosal neutralizing Ab [antibody] responses." (*see* page 2008, last sentence preceding the Discussion). Thus, at the time of filing of the present application and in the absence of the application's disclosure, a person having ordinary skill in the art would not have readily predicted which adjuvant in combination with a particular HIV envelope antigen would induce an immune response that is enhanced when compared with the immune response induced by the antigen in the absence of the adjuvant.

With respect to the rejection of the subject matter of former claim 9, which subject matter is presently recited in new claim 27, Applicants traverse this rejection and submit that '292 or the Lowell article in view of WO 95/11700, and further in view of VanCott and Desai fail to teach or suggest the claimed composition. As discussed in detail above, each of '292, the Lowell article, VanCott, and WO 95/11700 alone or in any combination, fails to teach

or suggest an immunogenic composition that comprises a truncated gp160 protein that is truncated at the C-terminal end. Furthermore, each of 292, the Lowell article, VanCott, WO 95/11700 and Desai fail to teach that the truncated gp160 protein may consist essentially of the amino acid sequence set forth at residues 33-681 of SEQ ID NO:1. Thus, each of the cited documents, alone or in any combination, fails to teach or suggest that this truncated gp160 lacks the terminal 187 amino acids residues of the transmembrane gp41 moiety of gp160 and that the gp41 moiety, therefore, has 159 amino acids (*see, e.g.,* specification, page 21, lines 27-30). Desai instead explicitly teaches that the deduced amino acid sequence of the gp120 portion of a gp160 polypeptide described therein has 537 amino acids, and that the gp41 portion has 346 amino acids (*see, e.g.,* Desai, at page 8383 and Figure 2). Furthermore, none of the cited documents taken alone or in any combination teaches, suggests, or provides any motivation to modify the gp160 polypeptide taught in Desai to obtain the truncated gp160 protein as described in the present application and recited in the instant claims. Applicants submit that only by using impermissible hindsight can the Examiner assert that in the absence of the disclosure in the present application a person having ordinary skill in the art could successfully obtain Applicants' claimed compositions in view of the cited art.

Applicants therefore respectfully submit that a *prima facie* case of obviousness has not been established and that the claimed subject matter is nonobvious as required under 35 U.S.C. § 103. Applicants respectfully request that this rejection of the claims be withdrawn.

REJECTION UNDER JUDICIALLY CREATED DOCTRINE OF DOUBLE PATENTING

The Examiner rejects claims 3, 4, 9-17, 19, and 21-23 under the judicially created doctrine of double patenting as obvious over claims 1, 2, 5, 7, and 8 of U.S. Patent No. 5,726,292 ('292), further in view of either Anselem (WO 94/26255) or WO 95/11700 and further in view of VanCott and Desai as described in the Action with respect to the rejections under 35 U.S.C. § 103(a).

Applicants respectfully traverse this rejection and submit that the presently claimed subject matter is a nonobvious modification of the constructs claimed in '292 and is an

inventive contribution to the HIV immunotherapeutics art. As discussed in the above remarks regarding the rejections under 35 U.S.C. § 103(a), none of the cited documents, alone or together, teaches or suggests an immunogenic composition that comprises a truncated gp160 protein having a molecular mass of about 140 kDa that is truncated at the carboxy terminal end. Each cited document fails to teach or suggest that portions of the gp160 may be removed and that the remaining portion would be useful as an immunogenic composition when combined with proteosomes. Instead, each of the cited documents describes use of full-length gp160 as an immunogen or describes use of an unrelated antigen as an immunogen (see Lowell article). Moreover, none of the cited documents alone or in any combination provides any motivation, teaching, or suggestion to alter the gp160 polypeptide to achieve the claimed immunogenic composition.

The '292 patent points out that gp160 is a transmembrane polypeptide and further describes that the presence of a hydrophobic moiety, such as the transmembrane region of gp160, may be sufficient such that gp160 would form a complex with proteosomes (*see, e.g.,* column 13, lines 43-48; column 18, line 21; column 20, lines 12-16). Because the carboxy terminal truncation of gp160 in the transmembrane gp41 portion would remove one or more hydrophobic portions of transmembrane gp41, a person having ordinary skill in the art would reasonably expect that to complex the truncated gp160 polypeptide with proteosomes would require that an exogenous hydrophobic moiety be added to the truncated gp160 to anchor the polypeptide to the proteosomes. As described in the present application, however, the truncated gp160 polypeptide without an exogenous hydrophobic portion in combination with proteosomes and bioadhesive emulsions was an immunostimulating composition (*see, e.g.,* pages 50-51).

In the HIV art, the antigenicity of the *env* gene products, the precursor gp160 and the mature gp120 and gp41 polypeptides, has been long recognized, and so has the difficulty in identifying one or more epitopes of these envelope proteins that would be useful for immunizing humans against multiple subtypes of HIV (*see, e.g.,* VanCott, Introduction and references cited therein). Moreover, in the absence of the present application describing an immunogenic composition comprising the truncated gp160 polypeptide, as recited, for inducing a neutralizing

antibody response against HIV in a subject, a person having ordinary skill in the art would not reasonably expect to obtain Applicants' claimed invention. The nonobviousness of the presently claimed process is evidenced by VanCott et al. (*J. Immunol.* 160:2000-12 (1998), submitted herewith), who demonstrated that the combination of proteosomes with truncated gp160 was a significantly improved immunogenic composition compared with full-length gp160 complexed with proteosomes (*see* VanCott et al., page 2008, first column; page 2009, Table IV). In mice, full-length gp160 elicited neutralizing IgG and IgA that were detected in sera; however, only mice immunized with truncated gp160 (therein referred to as gp451) elicited neutralizing antibodies in mucosal secretions. VanCott et al. concluded that their findings demonstrated "the importance of both adjuvant and protein structure in eliciting mucosal neutralizing Ab [antibody] responses" (*see* page 2008, last sentence preceding the Discussion). Thus, at the time of filing of the present application and in the absence of the application's disclosure, a person having ordinary skill in the art would not have readily predicted which adjuvant in combination with a particular HIV envelope antigen would induce an immune response that is enhanced when compared with the immune response induced by the antigen in the absence of the adjuvant.

VanCott and Kalyanaraman et al. (*AIDS Res. Hum. Retroviruses* 4:319-29 (1988)), to which the Examiner refers, *explicitly* teach that the gp160 described therein is a full-length gp160 (*see, e.g.,* Kalyanaraman et al. at page 322-324; *see also* specification at page 21, lines 18-23). Accordingly, a person having ordinary skill in the art could have no reasonable expectation of successfully obtaining the claimed compositions on the basis of the teachings in VanCott in combination with any of the cited documents. Even assuming, *arguendo*, that a person having ordinary skill in the art were able to intuit from VanCott that an immunogenic composition may comprise a truncated gp160 protein as recited, a person having ordinary skill in the art would have no reasonable expectation that a truncated gp160 antigen could be combined with proteosomes and bioadhesive nanoemulsions to form an immunogenic composition useful for eliciting neutralizing anti-HIV antibodies that are present in one or more of vaginal secretions, intestinal secretions, lung secretions, and feces.

Applicants further submit that '292 or the Lowell article in view of Anselem or WO 95/11700, and further in view of VanCott and Desai fail to teach or suggest the claimed composition. Each of '292, the Lowell article, VanCott, Anselem, and WO 95/11700, fail to teach or suggest an immunogenic composition that comprises a truncated gp160 protein that is truncated at the C-terminal end. Furthermore, each of 292, the Lowell article, Anselem, VanCott, WO 95/11700, and Desai fail to teach that the truncated gp160 protein may consist essentially of the amino acid sequence set forth at residues 33-681 of SEQ ID NO:1. Thus, each of the cited documents fails to teach or suggest that this truncated gp160 lacks the terminal 187 amino acids residues of the transmembrane gp41 moiety of gp160 and that the gp41 moiety, therefore, has 159 amino acids (*see, e.g.,* specification, page 21, lines 27-30). Desai instead explicitly teaches that the deduced amino acid sequence of the gp120 portion of a gp160 polypeptide described therein has 537 amino acids, and that the gp41 portion has 346 amino acids (*see, e.g.,* Desai, at page 8383 and Figure 2). Furthermore, none of the cited documents teaches, suggests, or provides any motivation to modify the gp160 polypeptide taught in Desai to obtain the truncated gp160 protein as described in the present application and recited in the instant claims.

Accordingly, Applicants submit that the presently claimed subject matter is nonobvious and therefore does not unjustifiably extend the exclusivity of patent '292. Applicants respectfully request that this rejection be withdrawn.

Applicants respectfully submit that all claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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Enclosure:
Second Supplemental Information Disclosure Statement

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